SOX10

Cloning

Sox10 was first identified in E11.5 mouse embryos using RT-PCR with degenerate oligos targeting the high-mobility group (HMG) domain, named due to the ability of other HMG-containing proteins to migrate rapidly on SDS-PAGE. The Sry-like HMG box (SOX) gene family is a subset of HMG-domain proteins, originally named based on their homology in the HMG region with the testis-determining factor SRY (Wright et al., 1993).

The spontaneous mutant *Dominant megacolon (Dom)* exhibits white spotting and megacolon with dominant inheritance in heterozygotes, and embryonic lethality in homozygotes (Lane, 1982).

Positional cloning identified *Sox10* as the gene mutated in *Dom* mice. The *Dom* mutation was a guanine insertion, predicted to cause a frameshift 3 of the HMG domain, resulting in translation of 99 novel amino acids followed by premature termination that removes the transcriptional activation domain (Southard-Smith et al., 1998).

(Herbarth et al., 1998) independently showed *Sox10* is the gene mutated in *Dom* mice.

Rat *Sox10* was cloned (Kuhlbrodt et al., 1998a).

Cloning of *SOX10* human cDNA, following the identification of *Sox10* as the *Dom* locus, showed human *SOX10* encodes a 466 amino acid protein, and SSCP followed by sequencing identified 4 WS4 patients carrying heterozygous *SOX10* mutations (Pingault et al., 1998).

Genomic clone analysis and RACE PCR characterized the full-length human SOX10 and mouse *Sox10* genomic loci, and showed that they both encode a 466 amino acid protein and share 98% sequence identity at the amino acid level (Pusch et al., 1998).

Comparative sequence analysis supported the location of the *Sox10* initiation methionine within exon 3, rather than exon 1. Structural modeling of SOX10 harboring a mutation in the HMG domain showed that the mutation would cause structural changes that would alter the DNA binding site and therefore block DNA binding. Two new *SOX10* mutations in WS4 individuals were identified, both of which encoded C-terminal truncations located downstream from the HMG domain (Southard-Smith et al., 1999).